Remarks

Introduction

Claims 1-8, 12, 17-19, and 22-26 were pending. By way of this response, claims 1-4, 6 and 19 have been amended, and claim 5 has been cancelled without prejudice. Claim 1 has been amended to more clearly define the components of the agent, claims 2-4 and 6 have been amended to read more clearly in view of the amendments to claim 1, and claim 19 has been amended to specify the site of administration of the agent. Support for the amendments to the claims can be found in the application as originally filed, and no new matter has been added.

For example, support for the amendments to claim 1 can be found at least at page 10, lines 29-37; page 11, lines 8-19; page 23, line 1, to page 24, line 5. Support for the amendments to claims 2 and 3 can be found at least at page 23, lines 1-17. Support for the amendments to claims 4 and 6 can be found at least at Examples 2, 6, and 8. Support for the amendments to claim 19 can be found at least at Examples 3, 4, 6, 10 and 12.

Accordingly, claims 1-4, 6-8, 12, 17-19, and 22-26 are pending.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-8, 12, 17-19, and 22-26 remain rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite.

Applicant traverses the rejections as it relates to the present claims.

Claim 1 has been amended to recite that the agent comprises a botulinum toxin proteolytic domain, a botulinum toxin translocation domain coupled to the proteolytic domain, and a substance P component covalently coupled to the translocation domain and effective in binding to a substance P receptor. Applicant submits that claim 1 clearly and definitely recites the components of the agent to achieve the treatment of neurogenic inflammation pain.

Claim 19 has been amended by replacing the word "systemically" with --to a site of the pain--. Applicant submits that claim 19 is definite.

In view of the above, applicant submits that the claims satisfy the requirements of 35 U.S.C. § 112, second paragraph, and respectfully requests that the rejection of the present claims based on this statutory provision be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-8, 12, 17-19, and 22-26 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly not being enabled.

Applicant traverses the rejection as it relates to the present claims.

Applicant submits that the specification of the above-identified application properly and sufficiently describes how to make and use the present invention. For example, the specification describes the structural and functional features

of the agents recited in the present claims (see at least page 10, lines 29-37; page 11, lines 8-19; page 23, line 1, to page 24, line 5). In addition, the specification describes how to administer the agents to the patients to treat neurogenic inflammation pain, how much of the agents to administer, and how to determine if the treatment was successful (see at least page 26, line 30 to page 31, line 2, and the examples). Applicant submits that any additional experimentation that may be needed would simply be to optimize the methods disclosed and claimed in the above-identified application. Such additional experimentation is routine to persons of ordinary skill in the art.

Further, independent claim 1 has been amended to recite specific components of the agent administered to treat neurogenic inflammation pain. Applicant submits that the present claims recite the components which achieve the desired effect. Thus, applicant submits that the present claims are not unduly broad as suggested by the Examiner.

With regard to the Examiner's comments regarding working examples, it is well established that working examples are not required in a patent application if the specification contains a sufficient description of the invention so that one skilled in the art will be able to practice the invention without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed (MPEP § 2164.02). Applicant submits that the specification, taken as a whole, contains a sufficient description of the invention to permit a person of

ordinary skill in the art to practice the presently claimed invention without undue experimentation.

Information about the state of the art that is relevant to the analysis of whether undue experimentation would have been required concerns, whether those skilled in the art are sufficiently familiar with the methods needed to practice the invention . Applicant submits that a person of ordinary skill in the art is sufficiently familiar with methods of administering similar compositions, such as compositions containing a botulinum neurotoxin, to treat other conditions that any additional experimentation that may be needed negligible in order to practice the present methods. For example, as disclosed in the instant specification, neurotoxin formulations, such as BOTOX®, have been administered to patients to treat conditions such as cervical dystonia, glabellar lines, blepharospasm, strabismus, and spasticity. Thus, applicant submits that a person of ordinary skill in the art, given the state of the art, and the information provided in the above-identified application, would be able to administer the present agents to a patient to treat neurogenic inflammation in accordance with the present invention without undue experimentation.

Applicant further submits that the presently claimed methods are not complex and unpredictable when taken in view of the present specification. Botulinum toxin has been used clinically and experimentally to inhibit neurotransmitter release, such as acetylcholine release from cholinergic neurons. In addition, as described in the specification of the above-identified application, botulinum neurotoxins have been shown to

generally inhibit many exocytotic processes. These effects have been used to provide therapeutic treatments for numerous conditions involving undesirable amounts of neurotransmitter release from neurons.

The present claims are directed to methods of treating a condition involving release of inflammatory agents from cells that express substance P receptors. In other words, administration of the present agents results in the agents binding to substance P receptors on cells, and delivery of the proteolytic domain of the agent into the cell to reduce the release of inflammatory agents from the cell. Thus, applicant submits that it would not require undue experimentation given the teachings of the above-identified application to practice the present methods and to administer the present agents to inhibit inflammatory agent release from substance P receptor expressing cells, thereby treating neurogenic inflammation pain, which involves the release of inflammatory agents from such substance P receptor expressing cells.

In response to the Examiner's comments regarding arthritis as a neurogenic disease, applicant submits that neurogenic inflammation does play a role in certain types of arthritis, such as at least rheumatoid arthritis, osteoarthritis, and non-articular arthritis, such as fibromyalgia. For example, Levine et al., "The contribution of neurogenic inflammation in experimental arthritis", J. Immunol, 1985, 135(2 Suppl):843s-847s (Abstract is attached as **Exhibit A**) provides evidence that in an experimental model of arthritis, there is an increase in the density of substance P-containing nociceptive afferent neurons, and that injection of substance P into a joint

increases the severity of arthritis in that joint. In addition, as discussed in Salo, "The role of joint innervation in the pathogenesis of arthritis", Can J. Surg, 1999, 42:91-100 (**Exhibit B**), clinical observations indicate the existence of important interactions between the nervous system and joints involved by arthritis and injury. Neuropeptides, such as substance P, are present in free nerve endings in joints and are potent inflammatory mediators that can potentiate an inflammatory response, and are released into the joint and peri-articular tissues during inflammatory arthritis. In addition, substance P mRNA and peptide content in the dorsal root ganglia and dorsal horn of the spinal cord increase substantially after induction of experimental arthritis.

Thus, applicant submits that arthritis, as used in the above-identified application, is properly characterized as a condition that can be associated with a neurogenic inflammatory component.

In view of the above, applicant submits that the above-identified application discloses sufficient information to enable a person of ordinary skill in the art to practice the presently claimed methods. Thus, applicant submits that the present claims satisfy the requirements of 35 U.S.C. § 112, first paragraph, and respectfully requests that the rejection of the present claims based on this statutory provision be withdrawn.

Conclusion

In conclusion, applicant has shown that the present claims satisfy the requirements of 35 U.S.C. § 112. Therefore, applicant submits that the present claims, that is claims 1-4, 6-8, 12, 17-19, and 22-26 are allowable. Therefore, applicant respectfully requests the Examiner to pass the above-identified application to issuance at an early date. Should any matters remain unresolved, the Examiner is requested to call (collect) applicant's attorney at the telephone number given below.

Respectfully submitted,

Date: 6/16/05

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